

Effects of dexamethasone on postoperative cognitive dysfunction and delirium in adults following general anesthesia: a meta-analysis of randomized controlled trials

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Abstract

Background Several studies have investigated the effects of dexamethasone on postoperative cognitive dysfunction (POCD) or postoperative delirium (POD); however, their conclusions have not been consistent. So we conducted a meta-analysis to determine the effects of dexamethasone on POCD/POD in adults following general anesthesia. **Methods** Cochrane Central Register of Controlled Trials (CENTRAL, 2018, Issue 11 of 12) in the Cochrane Library (searched November 17, 2018); MEDLINE OvidSP (1946 to November 16, 2018); and Embase OvidSP (1974 to November 16, 2018) were searched for randomized controlled trials that evaluated the incidence of POCD/POD following dexamethasone administration, in adults (age ≥ 18 years) under general anesthesia. We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework to assess the quality of evidence. **Results** Five studies were included (three studies/1393 participants for the incidence of POCD, and two studies/809 participants for the incidence of POD). There was no significant difference between the dexamethasone group and the placebo group in terms of the incidence of POCD in 30 days after surgery (RR 1.00; 95% CI [0.51, 1.96], P = 1.00, I² = 77%) or in the incidence of POD (RR 0.95; 95% CI [0.60, 1.50], P = 0.81, I² = 0%). However, both analyses had some limitations, and we considered the quality of the evidence for the postoperative incidence of POCD and POD to be very low. **Conclusions** This meta-analysis revealed that prophylactic dexamethasone did not reduce the incidence of POCD and POD. However, additional large high-quality trials are still needed to determine the effects of dexamethasone on the incidence of POCD/POD in patients undergoing surgery.

1. Background

Postoperative cognitive dysfunction (POCD) and postoperative delirium (POD) are neuropsychological disorders that can occur following the administration of general anesthesia. POCD is one of the most common complications in both young and elderly patients [1]. The reported incidence of POCD varied with different surgeries and with the use of different evaluation methods. In 1998, a multinational research group investigated the occurrence of long-term POCD in elderly patients after major noncardiac surgery and found that POCD was present in 25.8% of patients 1 week after surgery, and in 9.9% of patients 3 months after surgery [2]. Evered et al reported that the incidence of POCD at day 7 post-surgery was 17% for total hip joint replacement surgery, and 43% for coronary artery bypass graft (CABG) surgery; The incidence of POCD at 3 months post-surgery for both groups combined was 17%, and this was independent of the type of surgery performed or the anesthetic protocol used [3]. POCD is subtle and can only be detected by several neuropsychological tests, which are performed before and after surgery [4]. POD is a transient disturbance of a patient's consciousness, attention, cognition and perception, which can last from a few hours to a few days and can fluctuate in severity. POD typically occurs 2 to 3 days after surgery [5]. A systematic review showed that the incidence of POD was about 11% to 51%, and that the prevalence increases with age [6]. POCD and POD are serious complications that are associated with longer hospital stays, delayed functional recovery, decreased quality of life, an increased risk of further complications, and mortality [7-9].

Unfortunately, there are still many gaps in our knowledge regarding the pathophysiology of POCD and POD, which hinder our attempts in their prevention and treatment. POCD and POD have been associated with many predisposing and susceptible factors. Predisposing factors including: age, medical comorbidities, preoperative cognitive, visual, and auditory impairment are well documented [10]. However, there is growing evidence that the brain's reaction to a peripheral inflammatory process may play a role in the development of POD/POCD. Dillon et al found that elevated preoperative and postoperative levels of C-reactive protein are associated with POD [11]. A

recent meta-analysis has suggested that high concentrations of inflammatory markers in peripheral circulation and cerebrospinal fluid (CSF) are associated with POCD/POD [12]. In addition, several studies have investigated the effects of dexamethasone on POCD/POD; however, their conclusions have not been consistent. Therefore, we have conducted a meta-analysis to evaluate the effects of prophylactic dexamethasone administration on the incidence of POCD/POD in adults following general anesthesia.

2. Methods And Materials

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13], and we used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework to assess the quality of evidence [14]. This study is registered with PROSPERO, 23 October 2018, number CRD42018114552.

2.1. Eligibility and exclusion criteria

We selected all of the studies that met the following eligibility criteria: (1) randomized controlled trials (RCT); (2) adults (≥ 18 years old) who underwent general anesthesia; (3) perioperative administration of intravenous dexamethasone in order to prevent POCD/POD (including administration during the preoperative, intraoperative, and postoperative periods) versus no interventions (no drug administered or placebo group), regardless of the dose administered; (4) the incidence of POCD/POD as a primary or secondary outcome; and (5) availability of the full text in English. We excluded studies in which administration of another drug was used in the control group, dexamethasone was administered by another route, and those with no available assessment tools to evaluate the incidence of POCD/POD.

2.2. Search strategy

We performed a systematic search of the Cochrane Central Register of Controlled Trials (CENTRAL, 2018, Issue 11 of 12) in the Cochrane Library (searched November 17, 2018); MEDLINE OvidSP (1946 to November 16, 2018); and Embase OvidSP (1974 to November 16, 2018). The search strategy is shown in Appendix 1. We also manually searched the references of the included studies and reviews for additional studies. The following sources of ongoing and unpublished trials were screened: www.controlled-trials.com and clinicaltrials.gov.

2.3. Endpoints

Primary outcomes: The incidence of POCD or POD according to the author's own definition; however, there is a need for an objective assessment tool for POCD/POD.

Secondary outcomes: (1) all-cause mortality at 30 days; (2) any postoperative complications; (3) the level of C-reactive protein (CRP) measured within the first 24 hours postoperatively; and (4) the duration of hospitalization (measured in days) and length of time in the intensive care unit (ICU) (measured in hours).

2.4. Study selection

After importing the search results into EndNote X9, two review authors (Li and Wang) independently screened the reports according to the predetermined inclusion criteria. Firstly, duplicate reports were removed, and the studies selected on the basis of the title and abstract. Subsequently, the full text was screened for compliance with the

inclusion criteria. Disagreement between Li and Wang was resolved through discussion and consensus with a third reviewer (Fang).

2.5. Data extraction and assessment of risk of bias in included studies

Li and Wang extracted data independently from eligible studies, using a pre-designed form. Disagreement between the two review authors was resolved through discussion and consensus with a third reviewer (Fang). Two review authors (Li and Wang) independently assessed risk of bias for each included study using the Cochrane Collaboration's tool [15]. We assessed each study according to the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. We rated the overall risk of bias of a study as low if all of the domains were "low risk," and high if one or more of the domains were identified as "high risk" or "unclear risk."

2.6. Synthesis of results

We used the Cochrane Review Manager 5 (RevMan5) for statistical analysis of the data. Only primary and secondary outcomes that we had defined in advance were used in our analysis. For those studies that did not report a mean and standard deviation, we did not hand and transformate the date, because we did not know if it was normally distributed [16, 17]. Dichotomous variable data (e.g., incidence of POCD/POD, all-cause mortality at 30 days, and any postoperative complications) were expressed as relative risk (RR) with 95% confidence intervals (CI), while continuous data (e.g., the level of C-reactive protein (CRP) and length of time in hospital and ICU) were reported as mean differences (MD) with 95% CI.

2.7. Assessment of heterogeneity and data synthesis

We used the Chi-square test and calculated the I^2 statistic to assess the heterogeneity of the studies. There was significant heterogeneity between the studies (Chi-square $P < 0.05$, and $I^2 > 60\%$). We explored the possible influence of clinical heterogeneity (e.g., the differences between participants, type of surgery, the doses and timing of dexamethasone administration) and methodological heterogeneity (e.g., the different assessment tools used and blinding) [15]. Therefore, we performed a subgroup analysis of cardiac surgery versus noncardiac surgery, low dose dexamethasone (≤ 0.2 mg/kg) versus high dose (> 0.2 mg/kg) in order to explore clinical heterogeneity. When considering clinical and methodological heterogeneity, we used the randomized effect model [18]. A P value < 0.05 was considered statistically significant. If it was inappropriate to undertake the meta-analysis, we instead carried out a descriptive analysis of the study.

2.8. Assessment of publication bias and sensitivity analysis

Where the number of included studies was more than 10, we assessed the risk of publication bias among the included studies based on a funnel plot. We performed the following sensitivity analysis to assess the stability of POCD/POD: (1) excluding reports with a high risk of bias; (2) using different models (the randomized effect model and the fixed effect model).

3. Results

3.1. Study selection

Details of the flow of retrieved results and study selection are shown in Figure 1. According to the pre-defined search strategy, we retrieved 4850 studies. After removing the duplicate studies, we screened the remaining 3230 studies based on the title and abstract. We then readed the full text of 23 studies for further assessment according to the inclusion criteria. No eligible studies were found by manual retrieval. Finally, 5 studies were included in our analysis. After searching the clinical trials registration platform, we identified two ongoing studies that will be assessed after they have been completed [19, 20].

3.2. Study characteristics

Table 1 shows the characteristics of the included studies. Four of the included studies involved cardiac surgery [21-24], while the remaining one involved microvascular decompression surgery [25]. A larger, multicenter placebo-controlled randomized clinical trial was excluded because it did not report the occurrence of POCD, and not all patients had been assessed by the available delirium assessment tools [26]. The participants' mean age in all of the included studies was over 60 years, except for 1 study [25]. Four studies used a two-arm design in comparing dexamethasone to placebo except 1, which used a three-arm design [25]. Three studies assessed the effects of dexamethasone on POCD [21, 23, 25], while two studies investigated the effects of dexamethasone on POD [22, 24]. Dexamethasone doses and the time of administration varied, as shown in Table 2. The definition and assessment tools for POCD/POD were also different (Table 2).

3.3. Risk of bias in included trials

The risk of bias in included studies is summarized in Figure 2 and Figure 3. One study was identified as "low risk" in all domains, three studies had an unclear risk of bias in one of the seven domains due to reporting bias, and one study had a high or unclear risk of bias in five of the seven domains.

3.4. Incidence of POCD

Three studies reported the incidence of POCD, in which data was reported as the number of participants. Fang reported the incidence of POCD at five days postoperatively, Glumac at six days postoperatively, Ottens at 1 month and also at 12 months postoperatively. In order to avoid double counting, we only selected the results reported 1 month after surgery. Fang used neurocognitive tests to assess the incidence of POCD, while Glumac and Ottens both used a battery of 5 neuropsychological tests, making their definitions of POCD different. This meta-analysis included 1393 participants, which accounted for 95% of the total 1460 enrolled participants. There was no significant difference in the incidence of POCD in 30 days after surgery between the dexamethasone group and the control group (RR 1.00; 95% CI [0.51, 1.96], $P = 1.00$, I² = 77%; Figure 4). We judged the quality of the evidence to be very low based on the GRADE framework: (1) two studies had a high risk of bias; (2) the definitions of the outcome and the assessment tools were different; (3) results were inconsistent; and (4) imprecision of result.

3.5. Incidence of POD

Two studies reported the incidence of POD, in which the data was reported as the number of participants. Mardani reported the incidence of POD at the preoperative day, followed by the first, second, and third postoperative days. In order to avoid double counting and given that POD typically occurs 2 to 3 days after surgery, we only selected the results reported on the third postoperative day. Sauer reported the incidence at a fixed time point on each of the first 4 postoperative days, and we selected the results reported on the third postoperative day. Mardani used the Mini-Mental State Examination (MMSE) to assess POD, Sauer used the Confusion Assessment Method (CAM)

adapted for the ICU (CAM-ICU). Meta-analysis showed that there was no significant difference in the incidence of POD between the dexamethasone group and placebo (RR 0.95; 95% CI [0.60, 1.50], $P = 0.81$, $I^2 = 0\%$; Figure 5). We deemed the quality of the evidence to be very low because: (1) the two studies had an “unclear risk” of reporting bias; and (2) imprecision of result.

3.6. Secondary outcomes

No studies reported the all-cause mortality at 30 days post surgery. One of the five included studies reported postoperative complications including: deep sternal wound infection, leg infection, sepsis, and pneumonia in addition to cardiac, cerebrovascular, respiratory, and renal complications. The study showed that there was no significant difference between the dexamethasone and control groups in postoperative complication rates. We consider the quality of the evidence for this outcome to be very low because of the limited evidence available, and the fact that the study was at high risk of bias.

Only one study reported the level of CRP, which was measured 12 hours after surgery and on the each of the first 3 postoperative days; the CRP level was lower in the dexamethasone group compared with the placebo group at all time points ($P < 0.001$). We deem the evidence for this outcome to be of very low quality based on the limited evidence available.

Two studies reported the duration of hospitalization (measured in days). Our meta-analysis showed that the use of dexamethasone reduced the length of hospital stay (MD -0.57 d; 95% CI [-1.08, -0.07], $P = 0.03$, $I^2 = 0\%$, Figure 6), but the difference was so small that it did not have a clinical significance. We considered the quality of the evidence for this outcome to be very low because of the limited evidence available, and imprecision of result.

Three studies reported the length of ICU stay. Mardani and Glumac reported the duration as the mean \pm SD. Sauer reported the duration as the median (interquartile range); this was 23 (20–24) hours in the dexamethasone group, and 22 (20–24) hours in the control group. We excluded Sauer, and conducted a meta-analysis showing that use of dexamethasone reduced the length of ICU stay (MD -13.75 h, 95% CI [-23.82, -3.68], $P = 0.007$, $I^2 = 34\%$, Figure 7). We deemed the quality of the evidence for this outcome to be very low because of the limited evidence available, and imprecision of result.

3.7. Subgroup analysis

We performed a subgroup analysis of cardiac surgery versus noncardiac surgery. For POCD, one study describes noncardiac surgery, while two studies describe cardiac surgery. We noted no difference in incidence of POCD between the dexamethasone and control groups when noncardiac surgery was excluded (RR 0.90, 95% CI [0.21, 3.77], $P = 0.89$, $I^2 = 87\%$; 439 participants, Figure 8). We also found no significant difference between subgroups ($P = 0.73$) as shown in Figure 8. For POD, the participants of all studies underwent cardiac surgery.

We also performed a subgroup analysis of low dose (≤ 0.2 mg/kg) versus high dose (> 0.2 mg/kg) dexamethasone. For POCD, Fang and Glumac administered a low dose of dexamethasone (≤ 0.2 mg/kg), Ottens administered dexamethasone at a dose of 1 mg/kg (maximum 100 mg). This subgroup analysis showed no significant difference in the incidence of POCD between the dexamethasone of low dose (≤ 0.2 mg/kg) and control groups (RR 0.76, 95% CI [0.29, 1.98]; 1115 participants, Figure 9). We noted no significant difference between subgroups ($P = 0.14$) as shown in Figure 9. For POD, one study administered 8 mg dexamethasone before

induction of general anesthesia, followed by 8 mg every 8 hours. In another study, dexamethasone was administered at a dose of 1 mg/kg (maximum 100 mg); thus, we did not conduct a subgroup analysis.

3.8. Assessment of publication bias and sensitivity analysis

Considering that the number of included studies was small, we did not conduct an assessment of publication bias. Based on the prior definition, there was only one study with a low risk of bias, so we did not conduct the sensitivity analysis based on the risk of bias. Sensitivity analyses using the fixed-effect model yielded stable results overall: (POCD: RR 1.10, 95% CI [0.89, 1.37]; POD: RR 0.95, 95% CI [0.60, 1.50]).

4. Discussion

This meta-analysis aimed to assess the effects of dexamethasone on POCD and POD in adults following general anesthesia. We found that prophylactic intravenous administration of dexamethasone did not reduce the incidence of POCD in the 30 days following surgery (RR 1.00; 95% CI [0.51, 1.96], $P = 1.00$, $I^2 = 77\%$) or POD (RR 0.95; 95% CI [0.60, 1.50], $P = 0.81$, $I^2 = 0\%$). Furthermore, our meta-analysis showed that the use of dexamethasone reduced the length of hospital stay (MD -0.57 d; 95% CI [-1.08, -0.07], $P = 0.03$, $I^2 = 0\%$), but the difference was so small that it did not have a clinical significance. Nevertheless, the results of our meta-analysis suggested that the length of ICU stay was shorter in the dexamethasone group than in the placebo group (MD -13.75 h, 95% CI [-23.82, -3.68], $P = 0.007$, $I^2 = 34\%$).

Although we included adults aged over 18, the participants' mean age in all of the included studies was over 60 years, except for 1 study [25]. It is likely that older patients are at higher risk of POCD/POD than younger patients, therefore evidence which is related to the incidence of POCD/POD in younger patients (< 60 years old) is still lacking. All studies recruited patients that were scheduled for cardiac surgery except for 1 [25], which included participants that underwent microvascular decompression; this may limit the applicability of the evidence. Consequently, we should be careful not to extrapolate its use to patients undergoing other types of surgery. However, when we excluded this study from the meta-analysis, we found that the direction of the evidence did not change. There are two ongoing studies that were found through the clinical trials registration platform that need to be followed-up once they have been completed. This may change the conclusion of this meta-analysis.

Only one study was found to have a "low risk" of bias in all domains, while the other four studies had a high or unclear risk of bias in at least one of the seven domains. Two studies did not register their clinical trials or have a published study protocol, so the risks of selective reporting bias were unclear. We used the GRADE framework to assess the quality of evidence. We considered the quality of the evidence to be very low for the incidence of POCD because of inconsistencies in results and imprecision of result. The inconsistencies might be explained by differences in types of surgery performed, the dose of dexamethasone administered, and the definitions and assessment tools used in the diagnosis of POCD. However, we found no reduction in heterogeneity when we conducted the subgroup analyses of cardiac surgery versus noncardiac surgery, and low dose (≤ 0.2 mg/kg) versus high dose (> 0.2 mg/kg) dexamethasone. We also deemed the quality of the evidence for the incidence of POD to be very low because: (1) the two studies were at "unclear risk" of reporting bias; (2) imprecision of the result. As the result relating to the incidence of POD mainly came from one study (weight 97.2%), and the wide confidence intervals of result.

The occurrence of POCD/POD results from the interaction of many predisposing factors and susceptible factors. At present, the lack of relevant research means that we do not yet know which factor may be of most importance. In many forms of delirium it is thought that the cerebral effects of the peripheral inflammatory response are key elements in the pathophysiology, and that the brain of aged patients is more sensitive to peripheral inflammation than the brain of younger patients [10]. In a [post hoc analysis](#) of data from patients undergoing elective cardiac surgery with [cardiopulmonary bypass](#), a high postoperative CRP was associated with POD [27]. Lei et al found that perioperative dexamethasone can reduce the level of postoperative CRP [28]. In addition, previous meta-analyses had shown that a single intravenous perioperative dose of dexamethasone was associated with lower pain scores, an opioid-sparing effect, and a requirement for less rescue analgesia for the treatment of intolerable pain [29]. Morrison et al found that inadequate analgesia was associated with delirium in frail older adults [30]. Therefore, it seems plausible that dexamethasone can reduce POD. However, this meta-analysis showed that there was no significant difference in the incidence of POCD/POD between the dexamethasone group and the control group. This may reflect the fact that a single intervention cannot fully influence the incidence of POCD/POD. We considered the quality of the evidence to be very low for the incidence of POCD/POD reported in the studies, and there was significant heterogeneity in the incidence of POCD; probably because of differences in type of surgery performed, the dose of dexamethasone administered, and the definition and assessment tool used for the diagnosis of POCD. This may indicate that we require more well-designed, high-quality studies that use uniform assessment tools, demonstrate uniform reporting of their results, and are consistent in the dose of dexamethasone administered.

We did not find any reviews exploring the effects of dexamethasone on POCD/POD. More recently, a meta-analysis was conducted on the adverse effects of dexamethasone in surgical patients; it found that dexamethasone did not increase the risk of postoperative infection, and that it was associated with a mild increase in glucose level [31]. Toner et al assessed the safety of glucocorticoids in noncardiac surgery patients and found no increase in the risk of infection, a clinically unimportant increase in the glucose value, and a lower CRP concentration, but no difference in length of hospitalization [32]. In our meta-analysis, only one study reported the level of CRP, and found it to be lower in the dexamethasone group compared with the placebo group ($P < 0.001$). Two studies reported the length of hospitalization (measured in days), which [revealed](#) that the use of dexamethasone reduced the length of hospital stay (MD -0.57 d; 95% CI [-1.08, -0.07], $P = 0.03$, $I^2 = 0\%$), but the difference was so small that it did not have a clinical significance.

Conclusion

Our meta-analysis is the first systematic review to confirm the effects of dexamethasone on the incidence of POCD/POD in adults following general anesthesia. This meta-analysis [revealed](#) that prophylactic dexamethasone did not reduce the incidence of POCD and POD. However, only 3 studies reported the incidence of POCD, and only 2 studies reported the incidence of POD. Moreover, further large high-quality trials are still needed in order to confirm the effects of dexamethasone on the incidence of POCD/POD in patients following surgery, which should also focus on the effects of dexamethasone on all-cause mortality at 30 days post-surgery, postoperative complications, the level of CRP and on the duration of hospitalization and ICU stay.

Abbreviations

POCD: postoperative cognitive dysfunction, POD: postoperative delirium, GRADE: Grading of Recommendations, Assessment, Development and Evaluations, CABG: coronary artery bypass graft, CSF: cerebrospinal fluid, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT: randomized controlled trials, CRP: C-reactive protein, ICU: intensive care unit, RR: relative risk, CI: confidence intervals, MMSE: Mini-Mental State Examination, CAM: Confusion Assessment Method, CAM-ICU: Confusion Assessment Method adapted for the ICU, MD: mean differences.

Declarations

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Availability of data and material

All data generated or analysed during this study are included in this published article.

Authors' contributions

LLL participated in the design, collected the data, performed the quality assessment and statistical analyses. ZHZ participated in the design and draft the manuscript. WC and FMD collected the data, performed the quality assessment, and helped to draft the manuscript. XHY, LHL helped to perform statistical analyses and search strategy. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not available.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Reference

- [1] Monk TG, Price CC. Postoperative cognitive disorders. *Curr Opin Crit Care*. 2011; 17(4):376-81.
- [2] Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet*. 1998; 351(9106):857-61.

- [3] Evered L, Scott DA, Silbert B, et al. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesth Analg.* 2011; 112(5):1179-85.
- [4] Steinmetz J, Rasmussen LS. Peri-operative cognitive dysfunction and protection. *Anaesthesia.* 2016; 71 Suppl 1:58-63.
- [5] Robinson TN, Raeburn CD, Tran ZV, et al. Postoperative delirium in the elderly: risk factors and outcomes. *Ann Surg.* 2009; 249(1):173-8.
- [6] Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014; 383(9920):911-22.
- [7] Steinmetz J, Christensen KB, Lund T, et al. Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology.* 2009; 110(3):548-55.
- [8] Crocker E, Beggs T, Hassan A, et al. Long-Term Effects of Postoperative Delirium in Patients Undergoing Cardiac Operation: A Systematic Review. *Ann Thorac Surg.* 2016; 102(4):1391-9.
- [9] Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of Delirium and Other Major Complications on Outcomes After Elective Surgery in Older Adults. *JAMA Surg.* 2015; 150(12):1134-40.
- [10] Steiner LA. Postoperative delirium. Part 1: pathophysiology and risk factors. *Eur J Anaesthesiol.* 2011; 28(9):628-36.
- [11] Dillon ST, Vasunilashorn SM, Ngo L, et al. Higher C-Reactive Protein Levels Predict Postoperative Delirium in Older Patients Undergoing Major Elective Surgery: A Longitudinal Nested Case-Control Study. *Biol Psychiatry.* 2017; 81(2):145-53.
- [12] Liu X, Yu Y, Zhu S. Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. *PLoS One.* 2018; 13(4):e0195659.
- [13] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009; 339:b2700.
- [14] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008; 336(7650):924-6.
- [15] Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011. Available from www.cochrane-handbook.org.
- [16] Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol.* 2005; 5:13.
- [17] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol.* 2014; 14: 135.
- [18] Shuster JJ, Walker MA. Low-event-rate meta-analyses of clinical trials: implementing good practices. *Stat Med.* 2016; 35(14):2467-78.

- [19] Glenn S. Dexamethasone and Postoperative Delirium. <https://clinicaltrials.gov/ct2/show/NCT02109081?term=dexamethasone&cond=Delirium&rank=1> (first received 9 April , 2014). NCT02109081]
- [20] Wang DX. Dexamethasone, Flurbiprofen Axetil and Delirium After Lung Cancer Surgery. <https://clinicaltrials.gov/ct2/show/NCT03200600?term=dexamethasone&cond=Delirium&rank=2> (first received 27 June , 2017). NCT03200600]
- [21] Glumac S, Kardum G, Sodic L, et al. Effects of dexamethasone on early cognitive decline after cardiac surgery: A randomised controlled trial. Eur J Anaesthesiol. 2017; 34(11):776-84.
- [22] Mardani D, Bigdelian H. Prophylaxis of dexamethasone protects patients from further post-operative delirium after cardiac surgery: A randomized trial. J Res Med Sci. 2013; 18(2):137-43.
- [23] Ottens TH, Dieleman JM, Sauer AM, et al. Effects of dexamethasone on cognitive decline after cardiac surgery: a randomized clinical trial. Anesthesiology. 2014; 121(3):492-500.
- [24] Sauer AM, Slooter AJ, Veldhuijzen DS, et al. Intraoperative dexamethasone and delirium after cardiac surgery: a randomized clinical trial. Anesth Analg. 2014; 119(5):1046-52.
- [25] Fang Q, Qian X, An J, et al. Higher dose dexamethasone increases early postoperative cognitive dysfunction. J Neurosurg Anesthesiol. 2014; 26(3):220-5.
- [26] Dieleman JM, Nierich AP, Rosseel PM, et al. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA. 2012; 308(17):1761-7.
- [27] Burkhart CS, Dell-Kuster S, Gamberini M, et al. Modifiable and nonmodifiable risk factors for postoperative delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2010; 24(4):555-9.
- [28] Lei YT, Xu B, Xie XW, et al. The efficacy and safety of two low-dose peri-operative dexamethasone on pain and recovery following total hip arthroplasty: a randomized controlled trial. Int Orthop. 2018; 42(3):499-505.
- [29] Waldron NH, Jones CA, Gan TJ, et al. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2013; 110(2):191-200.
- [30] Morrison RS, Magaziner J, Gilbert M, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci. 2003; 58(1):76-81.
- [31] Polderman JAW, Farhang-Razi V, Van Dieren S, et al. Adverse side effects of dexamethasone in surgical patients. Cochrane Database of Systematic Reviews. 2018; 8:CD011940.
- [32] Toner AJ, Ganeshanathan V, Chan MT, et al. Safety of Perioperative Glucocorticoids in Elective Noncardiac Surgery: A Systematic Review and Meta-analysis. Anesthesiology. 2017; 126(2):234-48.

Tables

Table 1 the characteristics of the included studies

Studies ID	Design	Country	Age(min±SD)	M/F	Type of surgery	Outcome	
			Dex	Control	Dex	Control	
Fang 2014	3-arm RCT	China	48.9± 5.35a	48.0± 5.77	247/388	121/198	microvascular decompression POCD
Glumac 2017	2-arm RCT	Croatia	63.7± 9.0	64.2± 9.4	63/22	64/20	Cardiac surgery POCD
Mardani 2013	2-arm RCT	Iran	64.5± 11.10	60.04± 12.77	36/7	44/6	Cardiac surgery POD
Ottens 2014b	2-arm RCT	The Netherlands	63.4± 12.3	65.4± 11.5	103/37	109/29	Cardiac surgery POCD
Sauer 2014b	2-arm RCT	The Netherlands	67±12	66±12	255/112	225/145	Cardiac surgery POD

SD= standard deviation, POCD= postoperative cognitive dysfunction, POD= postoperative delirium, Dex=dexamethasone. aThis 3-arm RCT reported the age was 48.9±5.35, 48.0±5.60 in dexamethasone 0.1mg/kg and dexamethasone 0.2mg/kg respectively. bOttens 2014 and Sauer 2014 were two substudies of a larger, multicenter placebo-controlled randomized clinical trial.

Table 2 Characteristics of intervention and outcomes

Study ID	Dexamethasone doses	control	Time of intervention or control	POCD/ POD assessment method	POCD/POD definition	Assessment time
Fang 2014	D1:0.1 mg/kg D2:0.2 mg/kg	NS	before induction of anesthesia	Neuro-Psychological test battery	An individual whose postoperative performance deteriorated by 1 or more SDs on 2 or more tests was classified as having experienced early POCD.	the day before and On the fifth postoperative day
Glumac 2017	0.1 mg/kg	NS	10 h before the surgery	a battery of five neuropsychological tests	Authous calculated the Jacobson and Truax Reliable Change Index (RCI) for each patient in the dexamethasone and placebo groups. POCD in an individual is defined as an RCI equal to or less than $S1.96$ on at least one test	on the 6th day after the surgical procedure
Mardani 2013	8 mg DEX intravenous before induction of anesthesia followed by 8 mg every 8 h for 3 day.	NS	before induction of anesthesia followed every 8 h for 3 day	MMSE	delirium disorder was diagnosed if DSM-IV criteria were met in a patient	Preoperative day (PROD), first, second, and third postoperative day.
Ottens 2014	1 mg/kg (maximum 100 mg)	NS	shortly after induction of general anesthesia	a battery of five neuropsychological tests	Authous calculated the Jacobson and Truax Reliable Change Index (RCI), they defined POCD in an individual patient as an RCI equal to or less than -1.96 , or Z-score equal to or less than -1.96 in at least two different tests.	1 day before surgery and 1 month and 12 months after surgery

Sauer 2014	1 mg/kg (maximum 100 mg)	NS	at the time of induction of anesthesia	CAM-ICU	POD: diagnosed by the Confusion Assessment Method (CAM) adapted for the ICU (CAM-ICU) .	The primary study outcome was the presence of delirium on any of the first 4 postoperativ- e days. 7 days a week at a fixed time point
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POCD= postoperative cognitive dysfunction, POD= postoperative delirium, NS: normal saline, MSSE = Mini-Mental State Examination, SD= standard deviation, RCI=Jacobson and Truax Reliable Change Index, CAM=Confusion Assessment Method, CAM-ICU=Confusion Assessment Method adapted for the ICU, PROD=Preoperative day..

Figures

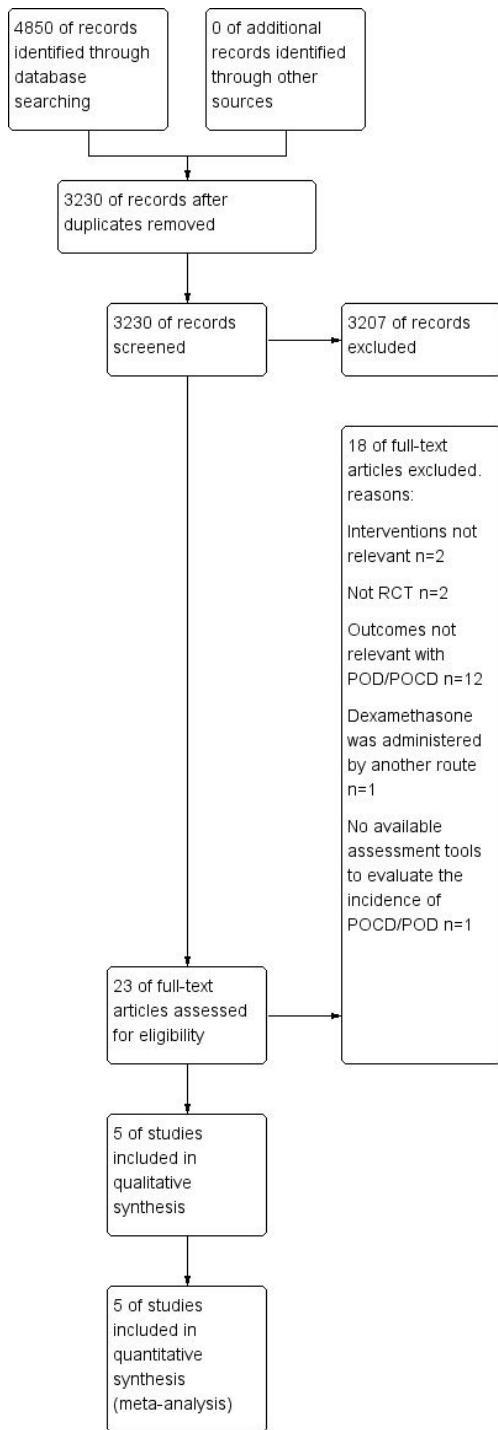


Figure 1

Study flow diagram.

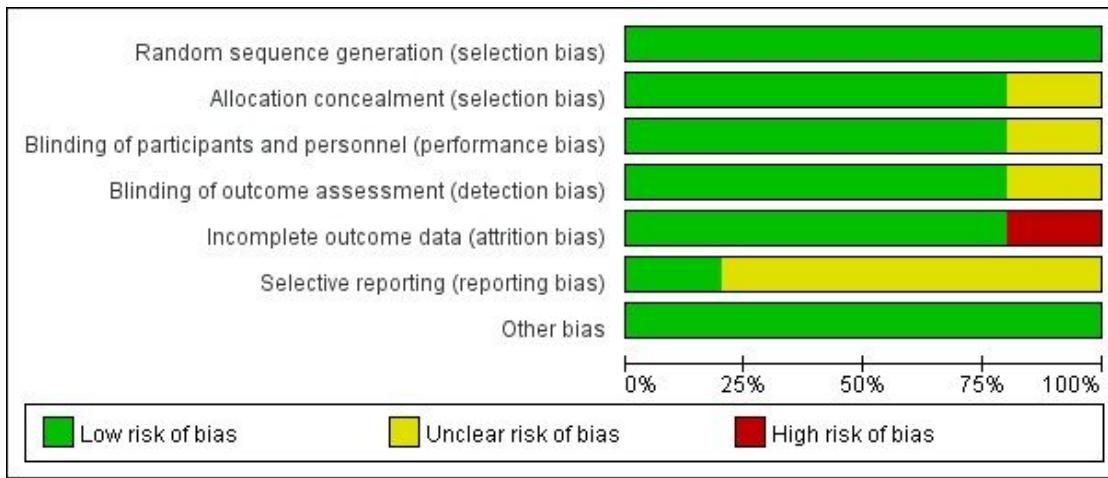


Figure 2

Risk of bias graph. Review authors' judgements about each risk of bias item presented as percentages across all included studies.

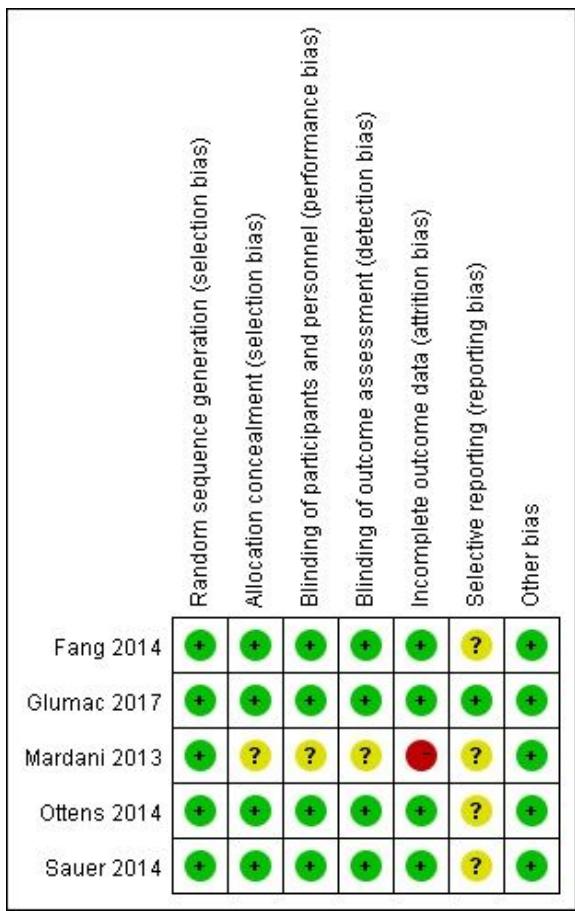


Figure 3

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

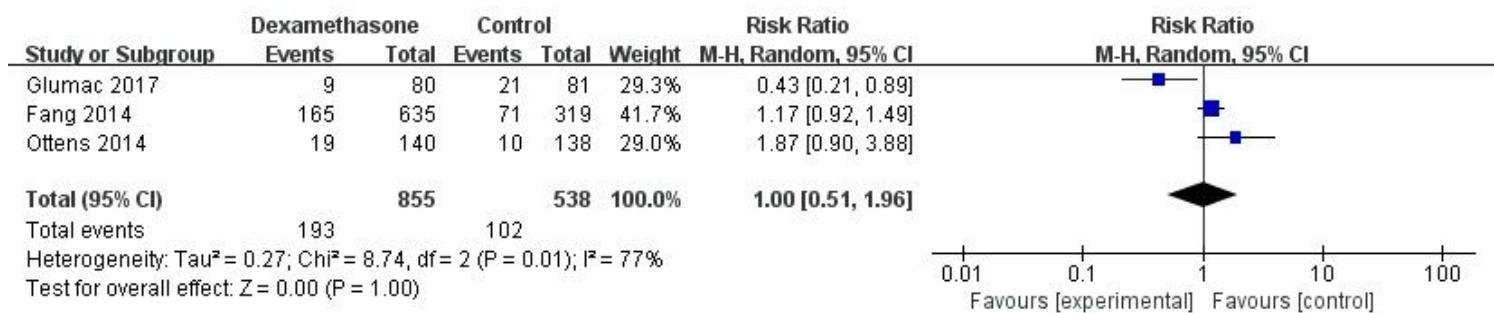


Figure 4

Forest plot of comparison: Dexamethasone vs Control, Outcome: POCD in 30 days after surgery.

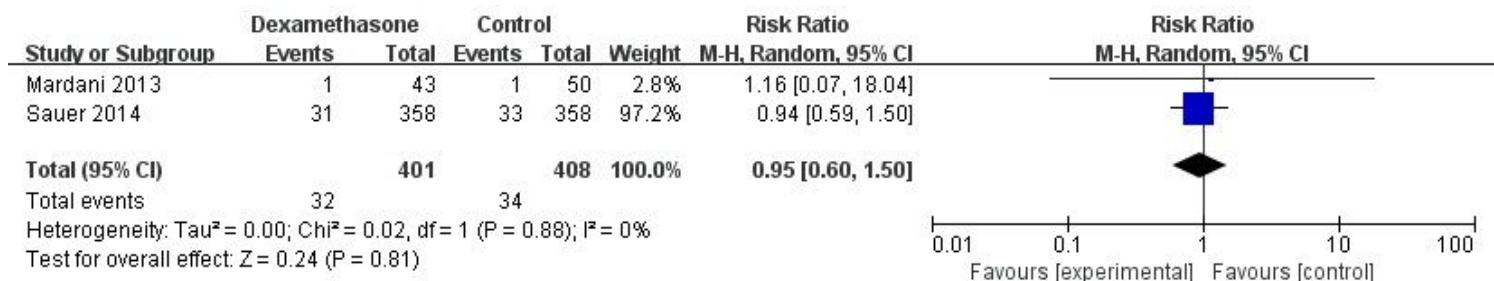


Figure 5

Forest plot of comparison: Dexamethasone vs Control, Outcome: POD.

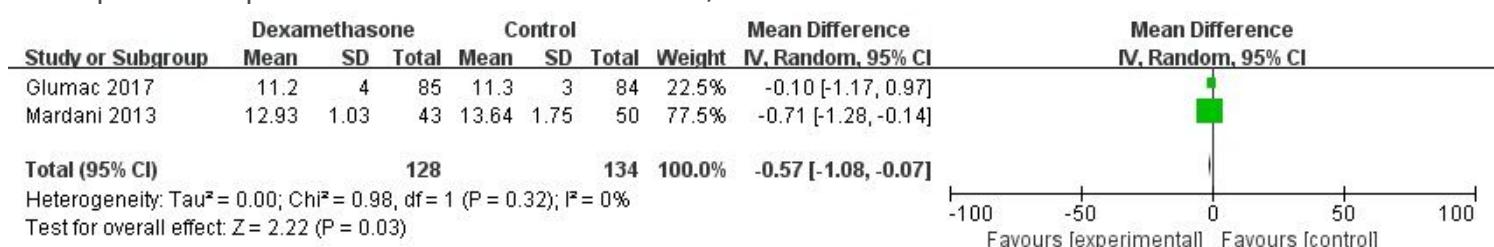


Figure 6

Forest plot of comparison: Dexamethasone vs Control, Outcome: Duration of hospitalization (measured in days).

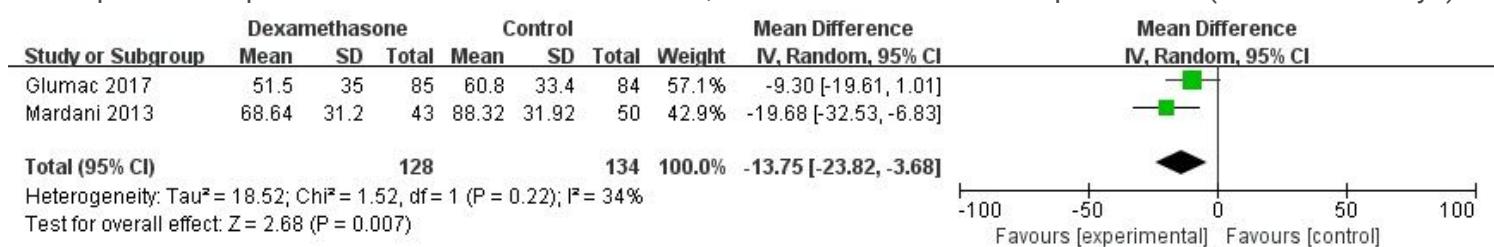


Figure 7

Forest plot of comparison: Dexamethasone vs Control, Outcome: Length of ICU stay (measured in hours).

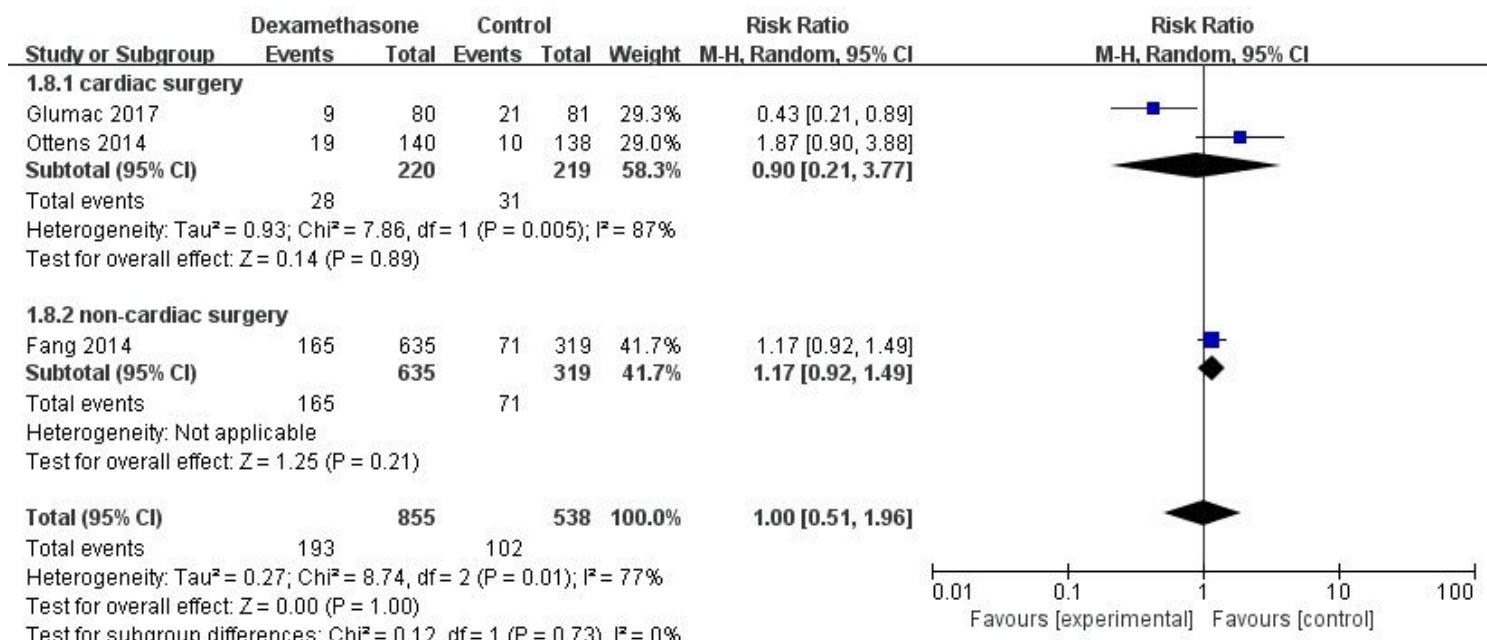


Figure 8

Forest plot of comparison: Dexamethasone vs Control, Outcome: Subgroup analysis of cardiac surgery versus noncardiac surgery.

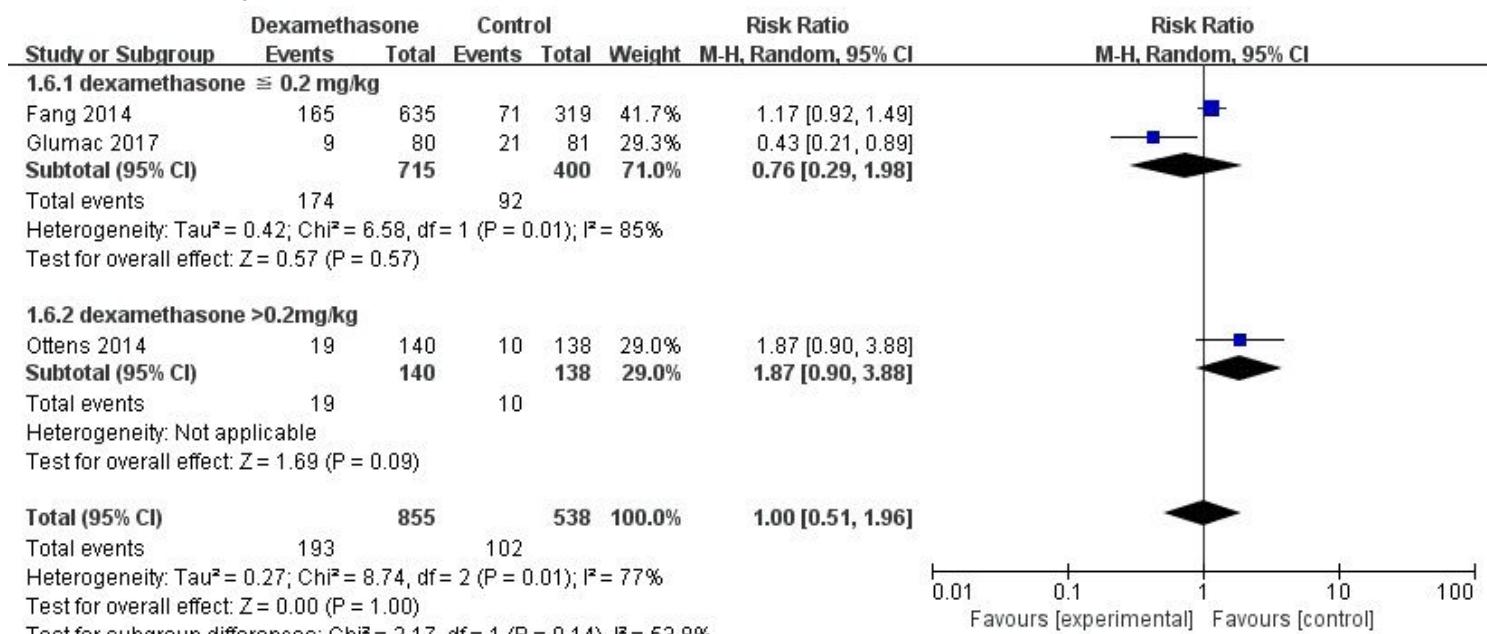


Figure 9

Forest plot of comparison: Dexamethasone vs Control, Outcome: Subgroup analysis of low dose ($\leq 0.2 \text{ mg/kg}$) versus high dose ($> 0.2 \text{ mg/kg}$) dexamethasone.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.doc